

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61F 13/00		A1	(11) International Publication Number: WO 93/20787 (43) International Publication Date: 28 October 1993 (28.10.93)
(21) International Application Number: PCT/US93/03088 (22) International Filing Date: 26 March 1993 (26.03.93)			(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(30) Priority data: 07/865,309 8 April 1992 (08.04.92) US 07/927,837 10 August 1992 (10.08.92) US			Published <i>With international search report.</i>
(71)(72) Applicants and Inventors: D'ANGELO, Joseph [US/US]; SCHUR, Henry [US/US]; 20 Northwest 181st Street, Miami, FL 33169 (US). (74) Agent: GREENBERG, Laurence, A.; Lerner and Greenberg, P.O. Box 2480, Hollywood, FL 33022-2480 (US).			
(54) Title: TRANSDERMAL DRUG DELIVERY SYSTEM			
<p>The diagram illustrates a multidose transdermal drug delivery system. It features a central laminate composite (1) with a rectangular shape. On top of this composite are several components: a small rectangular piece (2) at the bottom left, a larger rectangular piece (3) at the bottom right, a vertical strip (4) extending upwards from the center, and a curved strip (5) attached to the side. A small circular component (6) is positioned near the top edge. At the top right, there is a larger, irregularly shaped piece (8) which appears to be a unit dose or reservoir. A horizontal strip (10) runs along the right edge of the composite. A vertical strip (9) is attached to the side of the composite. A small rectangular piece (11) is located at the bottom left corner. A security strip (14) is shown at the bottom edge of the composite, spanning most of its width.</p>			
<p>(57) Abstract</p> <p>A multidose transdermal drug delivery assembly comprises a laminate composite having a plurality of reservoirs (7) formed therein. Unit doses with transdermal drug actives for transdermal administration are disposed in the reservoirs. Individual seals (5) enclose the drug in each of the reservoirs. The unit doses are in the form of a multiphase composition of microspheres wherein an internal phase comprises the drug actives and adjuvants surrounded by an outer phase of film-forming polysaccharides engrafted with transdermal promoters. The microspheres are distributed through a diffusible matrix for the composition. The individual seals (5), upon activation, disrupt the microspheres (8) to release the drug actives and adjuvants in the unit dose compartment (7), and the drug diffuses through the matrix to a patient's skin. A security strip (14) may be provided to prevent accidental activation of the drug.</p>			

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Burkin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LJ	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam

TRANSDERMAL DRUG DELIVERY SYSTEMBackground of the Invention:Field of the Invention:

5 This invention relates to transdermal medication assemblies, and particularly to patch assemblies for the transdermal administration of medicament.

Description of the Related Art:

Transdermal drug administration has recently come to the
10 forefront as a useful route for continuous dosing of useful drugs where other means of administration are either discontinuous, labor intensive or where other routes present absorption or inactivation problems. Whereas per os administration has been time honored i.e. "a teaspoonful three times
15 a day", such unit dose administration was subject to erratic blood levels of the actives due to non-uniform absorption from the gut due to other gut contents or inactivation of the drug actives by the digestion process or the normal action of the liver. In addition, the need for active periodic admin-
20 istration i.e. three times a day, required active and willing participation by the patient or in home or hospital settings by the caregiver i.e. mother or nurse.

All these shortcomings are obviated by transdermal applica-
tion where possible, of the drugs. A patch is adhered to a

clear area of the skin and the drug is continually absorbed through the skin into the bloodstream for systemic distribution.

The skin is particularly useful as it presents large areas for drug administration, the skin being the largest organ of the human body. The utility of such a mode of administration has been promoted with the discovery and development of a group of compounds that promote transdermal penetration of the various active drugs. Such compounds are known in the art as penetration enhancers. They are generally characterized to be from the group of monovalent branched or unbranched aliphatic, cycloaliphatic or aromatic alcohols of 4-12 carbon atoms; cycloaliphatic or aromatic aldehydes or ketones of 4-10 carbon atoms, cycloalkanoyl amides of C 10-20 carbons, aliphatic, cycloaliphatic and aromatic esters, N, N-di-lower alkylsulfoxides, unsaturated oils, terpenes and glycol silicates.

These compounds and their specific activity as penetration enhancers, are more fully discussed in the text "Transdermal Delivery of Drugs, A.F. Kydonieus (Ed) 1987 CRL Press and in such U.S. Patents as 4,913,905, 4,917,676 and 5,032,403.

As a result of these penetration enhancers, almost any drug, to some degree, can be administrated transdermally, as described, for instance, in U.S. Patents Nos. 4,917,676,

3,598,122; 3,598,123; 3,742,951; 3,797,494; 3,948,254; 3,996,734; 4,284,444; and 4,597,961. Examples of such pharmacological actives include administration of antibacterials such as the penicillins, tetracyclines, second and third generation cephalosporins, chloramphenicol sulfonamides; sedatives and/or hypnotics, such as barbiturates, carbromal, antitussives such as codeine and dextromethorphan; anti-anxiety drugs such as the benzodiazepines including diazepam, buspirone; psychostimulants such as imipramine, amitriptyline and other tricyclic anti-depressants; anti psychotic drugs and tranquilizers such as lithium, chlorpromazine and haloperidol, reserpine, thiopropazate; Parkinsonism control agents such as bromotriptine, percolide, the anticholinergics including benzotropine, procyclidine, amantadine (also an antiviral); hormones and hormone antagonists and agonists, including adrenocorticosteroids; insulin, androgenic steroids, estrogenic and pro-gestrogenic steroids, thyroxin and its agonist 5-FU (fluorouracil), tamoxifen; antipyretics and analgesics such as aspirin/acetaminophen and other non-steroidal anti-inflammatory drugs (NSAID), analgesics based on morphine; morphine antagonists; vasodilating agents such as nitro-glycerine, isorbide dinitrate; alpha and beta-blockers and other cardioactive drugs; antimalarials; antihistamines and anticholinergics including atropine, hyoscyamine or methscopolamine (for motion sickness; weaning agents such as nicotine for addiction to tobacco; and

antiasthmatic bronchodilators such as formoterol; and combinations of such pharmaceutical actives.

Of course, while feasible, not all of these actives have yet been completely tested for efficacy by transdermal administration but many are under vigorous scrutiny. Other actives at this time are not economically viable for such administration, as the cost of full safety testing is too great for the specific number of patients involved.

As can be seen from this background discussion and the history of this type of medication, it is apparent that application by transdermal patch is a useful form for administration of medication. However, a single dose per patch requires uneconomical repeated application.

Summary of the Invention:

It is an object of this invention to provide a multiple unit-dose transdermal patch assembly.

It is a further object of this invention to provide each unit dose in the multiple dose patch with an indicating means, visual or olfactory, to inform the wearer or attendant concerning the activation for administration of each unit dose in the multidose patch assembly.

It is another object, where a single application steady state dosing may not serve the best needs of the patient and is inconsistent with accepted clinical practice, to provide a method of multiple sequential dosing in those cases. Additionally, this invention allows for the variation, where needed, in dose levels within a single "patch".

A further object is to provide a patch which is secured against accidental release of the medicament. This object is attained by providing a security strip.

Yet a further object of the invention is to provide a patch which may readily be refilled or the medication of which may be varied by insertion of medicament through a filling septum.

With the foregoing objects of the invention in view there is provided, in accordance with the invention, a patch assembly which comprises a base in which the steady state dosage is contained in individual tear-and-release or pull-and-release reservoirs. The reservoirs contain the medicament which can be the same as contained in the base or various unit dosages of the base or entirely different synergistic medicaments.

In general, the invention pertains to transdermal medication assemblies comprising multiple unit-dose reservoirs with each reservoir having individual tear-and-release or pull-and-

release resealable closure means for initiation and administration of the medication.

Further objects and ancillary benefits will be apparent from the disclosure of the invention which pertains to a multiple unit-dose transdermal patch assembly.

With the foregoing objects of the invention in view there is provided, in accordance with one aspect of the claimed invention, a multidose transdermal drug delivery assembly, comprising a laminate composite of a drug-permeable membrane 10 to be placed in contact with a patient's skin; a transfer gel layer disposed on the membrane; a permeable membrane disposed on the transfer gel layer; overlaid impervious drug enclosure means for receiving and protectively enclosing a drug active to be transdermally administered; the drug enclosure means 15 and the permeable membrane defining a plurality of compartments therebetween defining reservoirs for respective unit doses of the drug active; and individual activation means for releasing unit doses of the drug active from respective ones of the compartments for contacting with the 20 patient's skin.

In accordance with added features of the invention, assembly includes means for enclosing the drug active in each of the reservoirs.

In accordance with a further feature of the invention, the assembly includes actuating means for controlling transdermal absorption of the drug active and means for adhesively securing the laminate composite to the patient's skin.

- 5 In accordance with an additional feature of the invention, the reservoirs have a periphery which is smaller than a periphery of the permeable membrane and a periphery of the overlaid impervious layer, so that the permeable membrane and the overlaid impervious layer extend outwardly of the
- 10 reservoir periphery.

In accordance with a further feature of the invention, the enclosing means are individual resealable strips disposed on the reservoirs for activating respective unit doses by peeling back respective ones of the strips. Also, the

- 15 enclosing means may be individual sealing strips disposed between the reservoirs and the permeable membrane, the strips being removable from the assembly through a resealing strip for activating respective unit doses.

In accordance with yet additional features of the invention,

- 20 the system includes means for indicating initiation of administration of a unit dose from a respective reservoir upon activation, which may be visual or olfactory signal means. In other words, the resealable closure means on each unit dose reservoir are preferably provided with indicia for

indicating that the unit dose has been released for administration. Among such indicia useful for indication of actuation and initiation of release of the unit dose, are colored stains or olfactory substances such as perfumes
5 released upon actuation of the unit dose seal.

In accordance with yet a further feature of the invention, the reservoirs comprise microencapsulations of the drug active, the drug active may be insulin encapsulated into capsules of substantially 1 to 150 microns diameter, the
10 microencapsulations are formed of a layer of polymer encapsulating the drug active, the polymer layer having drug-penetration moieties engrafted thereon; the moiety can be laurocapram; 1-dodecylhexahydro-2H-azepin-2-one.

In accordance with again an added feature of the invention,
15 the transfer gel includes medicament for steady state dosage transdermal delivery.

In accordance with again a further feature of the invention, the assembly includes a plurality of security strips disposed above each of the individual activation means for preventing
20 accidental activation of the drug active.

In accordance with again an additional feature of the invention, the compartments have openings in the form of fill ports formed therein for allowing introducing or withdrawing

medicament from the reservoirs, and including a sealing filling septum closing the fill ports.

With the objects of the invention in view, there is further provided, a multidose transdermal drug delivery assembly,
5 comprising a laminate composite having a plurality of reservoirs formed therein, unit doses with transdermal drug actives disposed in respective ones of the reservoirs for transdermal administration, individual seal means for enclosing the drug in each of the reservoirs, the unit doses
10 being in the form of a multiphase composition of microspheres wherein an internal phase comprises the drug actives and adjuvants surrounded by an outer phase of film-forming polysaccharides engrafted with transdermal promoters, the microspheres being distributed through a diffusible matrix
15 for the composition; the individual seal means having means for disrupting the microspheres upon activation of the seal means to release the drug actives and adjuvants in the unit dose compartment to diffuse through the matrix to a patient's skin. The laminate composite may include means for adhesively
20 securing to a patient's skin.

In accordance with a concomitant feature of the invention, the assembly includes indicating means being freed by the seal means for signalling initiation and administration of the unit dose from each individual reservoir, and means for preventing accidental release of medicament.
25

The laminate composite forming reservoirs for the drug actives and associated vehicles may be formed from flexible or rigid materials. Useful impervious materials include fabrics impregnated with film rendering the fabrics 5 impervious to the drugs and vehicles, regenerated cellulose (cellophane), ABS polymer/cellulose acetate, ethyl cellulose, copolymers of plasticized vinylacetate-vinylchloride, polyethylene terephthalate; polyethylene, polypropylene, nylon film or nylon fabric impregnated with drug impervious films, 10 polyvinylidene chloride, impregnated and coated papers and metallic foils, metalized shaped films of PVC, ABS and other shapeable polymeric sheets or films.

The unit dose reservoirs of the assembly may be impressed or molded into the polymeric and impregnated materials or they 15 may be formed by sealing the peripheries of impervious material layers to form pouches which, upon loading through openings, will become drug reservoirs. Useful dimensions for the patch are approximately 2.5 cm by 5.0 cm and up to about one 5 to 15 mm in thickness. The size of each reservoir is 20 determined by the volume of the unit dose to be administered. The volumes exemplified are sufficient for most unit doses for transdermal delivery of the drugs, but larger or smaller volumes may be used. The drugs and their adjurants are dissolved, suspended, absorbed or contained in matrices or 25 solutions. Useful matrices are gels of biopolymers i.e. alginates, gelatins, chitin, PVP, etc..

While the examples above disclose rectangular reservoirs, as they permit adjacent positioning of individual unit doses in a multiple dose assembly, the reservoirs in pouch or container form may also be circular, oval or irregular in form

- 5 depending on positioning of the assembly on the body or limbs. Configuration of the assembly is dictated by the ultimate positioning of the assembly in areas where adhesion, absorption, and contact with clothes, limbs and body hair are to be taken into account.

- 10 The number of unit doses included in each assembly depends on the size of the reservoirs to configure a convenient size. Generally, four to ten unit doses are convenient with seven units preferred as permitting a single application of the drug once a day, or several times a day depending on the
15 medicament and clinical application.

The principle of single unit doses in the multiple dose assembly is particularly useful as only a limited amount of the drug actives is exposed to the skin for transdermal absorption. When non-segregated multiple doses, as taught by
20 the prior art are used, there arise problems.

This invention includes the various drugs that can be delivered in unit doses, configurations of such assemblies, storage of the drugs within the assembly and includes delivery systems to the skin for the drugs from storage areas

in the assembly; various systems for activating each unit-dose of the assembly, and various means for indicating activation of each unit-dose.

A variant reservoir, which is a novel aspect of this invention comprises the microencapsulation of the drug actives in 5 a biocompatible polymer to protect the drug from ambient degradation as well as to serve as a reservoir for the dosage volume. Insulin is an example of such a drug active. A specific advantage for the encapsulation of the drug in such 10 a polymer is that it allows for the controlled rate of release of the medicament by adjustment of the crosslinking, density and specific type of polymer selected for the encapsulation.

In addition, passage of the relatively large molecule of the 15 exemplified insulin as well as other hormones, enzymes and proteins through the skin has been found to require some method of penetration enhancement. Several chemicals alone or in combination with certain solvents have been noted to promote transdermal penetration. It has been suggested that 20 some of these materials perform their penetration by enlarging the interstitial spaces between the cells of the dermis. Such penetration vehicles or enhancers are known to the art and many are mentioned in the afore-mentioned "Transdermal Delivery of Drugs".

Suitable penetration enhancers (such enhancers are preferably monovalent, saturated or unsaturated aliphatic, cycloaliphatic or aromatic alcohols having from 4 to 12 carbon atoms, e.g. n-hexanol or cyclohexanol, aliphatic,

5 cycloaliphatic or aromatic hydrocarbons having from 5 to 12 carbon atoms, e.g. hexane, cyclohexane, isopropylbenzene and the like, cyclo-aliphatic or aromatic aldehydes and ketones having from 4 to 10 carbon atoms, such as cyclohexanone, acetamide, N,N-di-lower alkylacetamides such as N, N-

10 dimethylacetamide or N, N-diethyl-acetamide, C₁₀-C₂₀-alkanoylamides, e.g. N, N-dimethyllauroylamide, 1-n-C₁₀-C₂₀-alkylazcycloheptan-2-one, e.g. 1-n-dodecylazacycloheptan-2-one(Azone® laurocapram), or N-2-hydroxyethylacetamide, and known vehicles and/or penetration enhancers such as aliphatic, cycloaliphatic and aromatic esters N, N-di-lower alkylsulphoxides, unsaturated oils, halogenated or nitrated aliphatic or cycloaliphatic hydrocarbons, salicylates, polyalkylene glycol silicates, and mixtures thereof.

15

20 Example:

The preferred penetration enhancer for use with micro-encapsulated insulin is the aforementioned Azone® laurocapram or 1-n-dodecylazacycloheptan-2-one because, in addition to being compatible to concentrated insulin, it is a lipophylic material.

25

The microencapsulation of insulin is done at low temperature i.e. below about 40°C. The insulin is solubilized at the desired concentration in a normal buffered saline (0.9N NaCl) solution of sodium alginate. The final solution contains 95% 5 insulin. The mixture is slowly stirred to ensure uniformity and the microcapsules are formed by the conventional ultrasonic spraying into a conventional suitable crosslinker. While other methods may be utilized, the ultrasonic dispersant method produces a very uniform and controlled sphere 10 size in a short time. Microencapsulating cross-linkers for sodium alginate may be polycations or polyanions. A Chitosan solution, as crosslinker, will produce uniform hard shell porous microcapsules of 150 microns or less depending on ultrasound frequency during spraying. Other methods of drop 15 formation may be employed as known in the art such as by gravity, drop tube or air sprays. The size of the microcapsules is less than 150 microns with various ranges 1 to 150 microns being used depending on desired concentrations of the drugs to be administered.

20 The techniques of microencapsulation have been disclosed in U.S. Patents Nos.

3,161,602	3,270,100	3,341,466	4,391,909
3,396,117	3,405,070	3,567,650	
3,875,074	4,145,184	4,277,364	

They are incorporated herein by references.

The microcapsules, after washing in saline and dewatering, may be re-encapsulated to reinforce their strength by use of known hard shell systems using gelatin, methylmethacrylate, chitin etc. as used in the microencapsulating of inks and perfumes. However, before the re-encapsulation, the invention includes the engrafting to the microcapsule-forming biopolymer, the penetration enhancer moiety, particularly Azone®. The microcapsules are coupled to the Azone® by combining a polymer matrix of and glycerine with the Azone® to a 1-10% polymer matrix and then reacting therewith, by contact, the microcapsules under temperatures slightly above room temperatures. The "so-grafted" polymer matrix capsules are then overlaid to reinforce them or may be directly utilized by introduction into the reservoir.

Other dermal penetration or absorption enhancers may be added to a gel matrix in which the engrafted microcapsules are incorporated.

It is preferably a hydrogel through which the insulin can rapidly diffuse. The absorption enhancers include surface tension modifiers for the gel matrix as well as detergents for preparing the epidermis. Also useful for inclusion are typical vasodilators including the pharmaceutically acceptable vasolidator, physalemin.

The hydrogel matrix containing the microencapsulated insulin is introduced into commercially available transdermal single patch applicators or into the afore-mentioned multi-dose transdermal patch assembly for unit dose application.

- 5 In animal tests, patches containing insulin, microencapsulated as above, have been applied to the shaved skin of a series of insulin-deficient animals and the microcapsules have been disrupted to free the insulin into contact with the shaved skin. Within 30 minutes, all animals
- 10 exhibited measurable insulin levels in the blood. By adjustment of insulin concentrations in the microcapsules, therapeutic blood levels could be realized.

The commercial test patches mentioned above, are prepared using the drug impervious fabric for forming the pouch

- 15 Scotchpak® Backing 1006, manufactured by 3M Corp.

The pouches were filled with the drug hydrogel through major openings in the layer to be applied to the skin. The openings were covered with a permeable film of Cotran® 9710 (3M corporation), a micro-porous polyethylene. The patch was

- 20 adhered to the shaved skin by the Cotran® 9872 (3M corp.) acrylate adhesives approved as a contact with the skin and commercially offered for transdermal patch adhesive. Other useful adhesives for adhering the patches to the skin are disclosed in U.S. Patent 3,797,494.

There is also disclosed a method for the inhibition of the formation of advanced glycosylation end-products in diabetics. The method essentially comprises the step of transdermally administering effective amounts of 5 aminoguanidine. In addition to the administration of insulin by transdermal application in the form of microcapsules, it is also useful to administer, transdermally, either from the same patch or reservoir or from an adjacent reservoir or compartment in the multiple assembly of this invention, an 10 effective amount of aminoguanidine to inhibit diabetic retinopathy. This form of retinopathy is a serious complication of diabetes and is not completely countered by insulin alone.

This retinopathy results from advanced glycosylation end- 15 products (AGEs) resulting from the improper metabolism caused by diabetes.

Aminoguanidine is an inhibitor of AGEs and has been shown by such inhibition, to mitigate the collagen crosslinking, caused by the AGEs, leading to the progressive ocular complications of diabetes. 20

The transdermal application of the aminoguanidine can be in the form of a gel-suspension of the aminoguanidine. It can also be introduced into the transdermal patches in frangible microcapsules in the manner described herein for insulin.

The microcapsules of aminoguanidine may be transdermally administered either admixed with microcapsules of insulin in the same patch or a patch reservoir or the aminoguanidine and the insulin may be admixed with the insulin prior to formation of the microcapsules.

It is also useful, under certain circumstances, to position the aminoguanidine matrix in a separate reservoir adjacent to the insulin-containing reservoir and either activating each reservoir separately or concurrently. The adjuvants useful for insulin are often also useful for the aminoguanidine.

Brief Description of the Drawings:

Fig. 1 is a perspective view of a multiple unit dose patch assembly of the invention;

Fig. 2 is a cross-sectional view through the assembly of Fig.

15 1;

Fig. 3 is a perspective view of another embodiment of the transdermal patch assembly with filling ports and filling septa according to the invention; and

Fig. 4 is a cross-sectional view of the assembly of Fig. 3 along the plane X-X as seen in the direction of the arrows, additionally indicating a syringe for filling the medicament pouch through a fill port.

Description of the Preferred Embodiments:

Referring now to the figures of the drawing in detail and first, particularly, to Figs. 1 and 2 thereof, there is seen a multidose transdermal tear-and-release patch assembly 1,

- 5 comprising a laminate composite of layers forming individual unit cells 7 with each cell containing a layer of micro-encapsulated medicament 8. The assembly is a plurality of individual unit dose cells 7 having impervious walls separating each cell 7, from its respectively adjacent cell.
- 10 The unit cells 7 are filled with the desired medicament (drug actives) in microcapsule form 8. The unit cells 7 may also contain a gel-like matrix 18. The layer of microencapsulated medicament 8 is adhered to the bottom of a tear strip 5 and to the top of permeable membrane 13 by microcapsule adhesive
- 15 19.

The microencapsulated medicament 8 of each unit cell 7 may be identical or may be varied. The variation of the encapsulated medicament 8 may consist of differing strengths of the medicament which may be freed to the skin in response to

- 20 variations in the clinical condition. It is also possible to provide in adjacent cells 7, differing medicaments, for example insulin in one and aminoguanidine in the other. These medicaments are related to the individual condition for which the patch is prescribed and thus, such a combination
- 25 therapy is advantageous.

The unit dose cells 7 are closed to include the unit dose of encapsulated medicament 8 and gel matrix 18 by the overlaid tear strip 5 and the underlying permeable membrane 13. If necessary, the permeable membrane 13 may be utilized to control the rate of passage of encapsulated medicament 8 from the unit cell 7 into the transfer gel 11 after activation of the unit dose.

Each unit dose is activated by a two-step process. Step #1 is the removal of a security strip segment 2 by pulling back on 10 a tab 14, which thereby exposes a tear-and-release tab 3. The purpose of the security strip 2 is to prevent any accidental release of the medicament. In step #2, each unit dose is individually activated by pulling up the tear and release tab 3 located on the end of each tear strip 5. When the tear 15 strip 5 is pulled back to its attachment area 6, activation indicator 4 is released to provide the patient with a confirmation of the full activation of medicament 8. As the tear strip 5 is pulled back, the frangible medicament capsules are ruptured, thereby releasing the medicament 8, which diffuses through the permeable membrane 13, into the 20 transfer gel 11 and through a patch/skin interface membrane 12 and is ready for absorption into the skin. The skin patch interface membrane 12 may be completely pervious to the contents of the cell. The transfer gel 11 may or may not 25 contain a steady state medicament in appropriate dosage as required by the individual patient.

The tear strip 5 is secured to the unit dose 7 by an attachment area 6 where it is hinged at that point. In addition, it is adhered to the periphery of the unit dose 7 by a reservoir perimeter adhesive 9, which serves as the seal 5 for unit dose 7. The tear strip 5 is provided with sufficient peripheral surface for reclosure of unit dose 7 by repositioning the tear strip 5 on the assembly 1 via reservoir perimeter adhesive 9.

The entire assembly is fastened to the skin by an adhesive 10 border 10 which is adhesive coated to ensure positioning on the skin. The adhesive border 10 is preferably formulated to allow for repositioning of the assembly.

Referring to Figs. 3 and 4, which show a multi-unit dose transdermal pull pouch assembly 20, comprising a laminate 15 composite of layers forming individual medicament drug wells 21 containing medicament 22 in a plurality of forms, including but not limited to liquid, gel, microencapsulation or gas. The assembly 20 defines a series or plurality of individual dose medicament wells 21 having impervious walls 20 separating each medicament well from its adjacent well. The medicament within each well 21 may be identical or may be varied, as mentioned in the context of the embodiment of Figs. 7 and 8. The pull pouch medicament 22 is closed within the medicament well 21 by an overlaid drug impervious support 25 24 and an underlying impervious pull pouch strip 16.

Each unit dose of medicament is activated by a two-step process, similar to that explained in the context of Figs. 1 and 2. Step #1 is the removal of the security strip segment 2 by pulling back on its tab 14, which thereby exposes pull pouch tab 15. The purpose of the security strip is to prevent any accidental release of the medicament. In step #2 each unit dose is individually activated by pulling on pull pouch tab 15 until pull pouch strip 16 is removed from the assembly 20. Removal of the impervious pull pouch strip 16 allows the pull pouch medicament 22 to diffuse through the permeable membrane 13, into the transfer gel 11 and through the patch/skin interface membrane 12 and is ready for absorption into the skin.

The pull pouch strip 16 is secured to assembly 20 at its posterior end 26 by adhesive 23. The posterior end 26 of the pull pouch strip 16 is perforated and will tear free from the pull pouch assembly 20 upon pulling on the pull pouch tab 15.

A basal attachment membrane 25 is disposed below the pull pouch strip 16, which membrane 25 has on its upper surface reservoir perimeter an adhesive 9. The adhesive extends from the perimeter of the medicament well 21 to the perimeter of the pull pouch strip 16. Above the pull pouch strip 16 is a drug impervious support 24 which has on its lower surface the reservoir perimeter adhesive 9; which adhesive extends from the perimeter of the medicament well 21 to the perimeter of

the pull pouch strip 16. Above the pull pouch strip 16 is a drug-impervious support 24 which has on its lower surface the reservoir perimeter adhesive 9, which adhesive extends from the perimeter of medicament well 21 to the perimeter of the
5 pull pouch strip 16. The upper and lower surfaces of the pull pouch strip 16, which come into contact with the reservoir perimeter adhesive 9 are made from a non-adhering material, thereby permitting the pull pouch strip 16 to be removed from the assembly 20 without affecting the adhesive which is above
10 and below it. The pull pouch strip 16 is manufactured from a non-adhesive material. Upon removal of the pull pouch 16 from the assembly 20, the reservoir perimeter adhesive 9 on the surfaces of the basal attachment or occulatory membrane
25 and the drug impervious support 24 adhere to one another
15 forming a complete seal and preventing any leakage of the medicament 22.

The basal attachment membrane 25 extends past the patch/skin interface membrane 12 providing a surface to attach the assembly 20 to the skin via the border adhesive to ensure
20 positioning on the skin. The adhesive is preferably formulated to allow for repositioning of the assembly.

If the medicament well 21 contains medicament in the microencapsulated form, pulling the pull pouch strip 16 from the assembly will rupture the microcapsules, thereby
25 releasing the medicament for diffusion to the skin.

- The pull pouch strip 16 may include indicators to show the release of medicament from the medicament well 21. Such indicators would alert the patient as to the activation state of the medicament within the individual dose unit of the assembly 20. Indicators may consist of pigments released from microcapsules as known in the art, olfactory signals similarly microencapsulated and released by removal of pull pouch strip 16 or visual indicators located on the pull pouch strip 16.
- 10 In an additional embodiment, the uppermost composite layer of the pull pouch assembly 20 has a fill port hole 27, above each medicament well 21, into which is placed or fitted a filling septum which allows for the aseptic introduction or withdrawal of medicament into or from the medicament well 21.
- 15 The preferred method for the introduction or withdrawal of medicament is by syringe and needle. The filling septum 28 provides both a method for the medicament to be introduced into the medicament well 21 and also self-seals and protects the medicament after it has been inserted. Individually covering each fill port 27 and filling septum 28 is a septum protector 29, which is to be removed prior to insertion of medicament. The medicament well 21 may or may not contain gel or other non-medicament or medicament components as required.

This assembly is advantageous as it allows for customizing of the medicament to meet specific clinical needs which will be obvious to those skilled in the healing arts.

Claims:

1. A multidose transdermal drug patch assembly, comprising a drug-impervious support impressed to form a multitude of compartments, said compartments forming reservoirs for unit doses of a drug active to be transdermally administered, individual means for resealably enclosing the drug active in each of said reservoirs, said individual enclosing means being removable to release the unit dose into contact with the skin of the patient and being actuatable to control the transdermal absorption of the drug actives.
2. The assembly according to claim 1, wherein said removable enclosing means include means for indicating initiation of administration of the unit dose from said reservoir upon removal of said enclosing means, said indicating means being one of visual and olfactory signal means.
3. The assembly according to claim 1, including means for adhesively securing said support to the skin of a patient.
4. The assembly according to claim 1, wherein said reservoir comprises microencapsulations of the drug active.
- 20 5. The assembly according to claim 4, wherein the drug active is insulin encapsulated into capsules of substantially 1 to 150 microns diameter.

6. The assembly according to claim 4, wherein the microencapsulations are formed of a layer of a biocompatible polymer encapsulating the drug active, said polymer layer having drug-penetration moieties engrafted thereon.
- 5 7. The assembly according to claim 6, wherein said moiety is laurocapram; 1-dodecylhexahydro-2H-azepin-2-one.
8. A multi-dose transdermal drug patch assembly, comprising a drug-impervious support having a plurality of reservoirs impressed therein for containing unit doses of a drug for 10 transdermal administration, transdermal drug actives contained in said impressed reservoirs, individual removable seal means for enclosing said drug within each said reservoir; the unit doses of said drug comprising essentially a multiphase composition of microspheres wherein an internal 15 phase comprises the drug actives and adjuvants surrounded by an outer phase of film-forming biocompatible polysaccharides engrafted with transdermal promoters, said microspheres being distributed through a diffusible matrix for said composition; and said individual seal means having means for disrupting 20 said microspheres, upon removal of said seal means, to release the drug actives and adjuvants in said unit dose compartment to diffuse through said matrix to the skin in contact with said reservoir.

9. A multidose transdermal drug delivery assembly,
comprising a laminate composite having

- a plurality of reservoirs formed therein,
- unit doses with transdermal drug actives disposed in
5 respective ones of said reservoirs for transdermal
administration,
- individual seal means for enclosing said drug in each of
said reservoirs,
- said unit doses being in the form of a multiphase
10 composition of microspheres wherein an internal phase
comprises the drug actives and adjuvants surrounded by
an outer phase of film-forming polysaccharides engrafted
with transdermal promoters, said microspheres being
distributed through a diffusible matrix for said
15 composition;
- said individual seal means having means for disrupting
said microspheres upon activation of said seal means to
release the drug actives and adjuvants in said unit dose
compartment to diffuse through said matrix to a
20 patient's skin.

10. The assembly according to claim 9, including indicating
means being freed by said seal means for signalling
initiation and administration of the unit dose from each
individual reservoir, and means for preventing accidental
25 release of medicament.

11. A medium for insulin administration to diabetics
essentially consisting of a transdermal patch, comprising a
laminate composite encompassing a dose of insulin for
transdermal application, said dose essentially consisting of
5 a unit dose of insulin encapsulated within frangible
microspheres, said insulin being an inner phase and being
encapsulated by a film-forming biocompatible polymer forming
a film-outer phase, said film having a transdermal
penetration promoter engrafted thereon, said support having
10 an opening formed therein providing access of the insulin
dose to the adhered skin upon frangible disruption of the
microspheres.
12. The patch according to claim 11, wherein said insulin-
containing frangible microcapsules have diameters substan-
15 tially in the range of 1 to 150 microns.
13. A method for transdermal insulin administration, which
comprises the steps of contacting the skin with unit doses of
insulin consisting of dosage amounts of frangible
microspheres of encapsulated insulin, said insulin
20 microspheres having an internal phase formed of insulin and
surrounded by an enclosing frangible outer phase of a
polysaccharide film having, engrafted thereon,
skin-penetrating moieties for promoting transdermal
absorption of the insulin upon a release thereof from said

microcapsules, and breaking the frangible outer enclosing phase of said microcapsules to release the insulin.

14. The transdermal patch assembly according to claim 11, including a series of adjoining reservoirs, each comprising
5 transdermal actives for diabetes wherein said actives are selected from the group consisting of insulin, aminoguanidine and mixtures thereof, said diabetic actives being microencapsulated for transdermal administration and being activated prior to application to the dermis by rupture of
10 said microcapsules.

15. The assembly according to claim 14, wherein said microencapsulated insulin and the aminoguanidine are contained in adjacent reservoirs and each reservoir is individually activated for serial or concurrent administration as
15 medically indicated.

16. The transdermal patch according to claim 11, wherein said transdermal penetration promoter is laurocapram engrafted on said biocompatible polymer film by graft polymerization.

17. The transdermal patch according to claim 11, wherein said
20 biocompatible polymer is in the form of polysaccharide and sodium alginate.

18. A multidose transdermal drug delivery assembly,
comprising a laminate composite of

- a drug-permeable membrane to be placed in contact with
a patient's skin;
- 5 - a transfer gel layer disposed on said membrane;
- a permeable membrane disposed on said transfer gel
layer;
- overlaid impervious drug enclosure means for
receiving and protectively enclosing a drug active to
10 be transdermally administered;
- said drug enclosure means and said permeable membrane
defining a plurality of compartments therebetween
defining reservoirs for respective unit doses of the
drug active; and
- 15 - individual activation means for releasing unit doses
of the drug active from respective ones of said
compartments for contacting with the patient's skin.

19. The assembly according to claim 18, wherein said
reservoirs have a periphery being smaller than a periphery of
20 said permeable membrane and a periphery of said overlaid
impervious layer, so that said permeable membrane and said
overlaid impervious layer extend outwardly of said reservoir
periphery.

20. The assembly according to claim 19, wherein said
25 enclosing means are individual resealable strips disposed on

said reservoirs for activating respective unit doses by peeling back respective ones of said strips.

21. The assembly according to 19, wherein said enclosing means are individual sealing strips disposed between said reservoirs and said permeable membrane, said strips being removable from said assembly through a resealing strip for activating respective unit doses.
22. The assembly according to claim 18, wherein said transfer gel includes medicament for steady state dosage transdermal delivery.
23. The assembly according to claim 18, including a plurality of security strips disposed above each of said individual activation means for preventing accidental activation of the drug active.
24. The assembly according to claim 18, wherein said compartments have openings in the form of fill ports formed therein for allowing introducing or withdrawing medicament from said reservoirs, and including a sealing filling septum closing said fill ports.

FIGURE 1

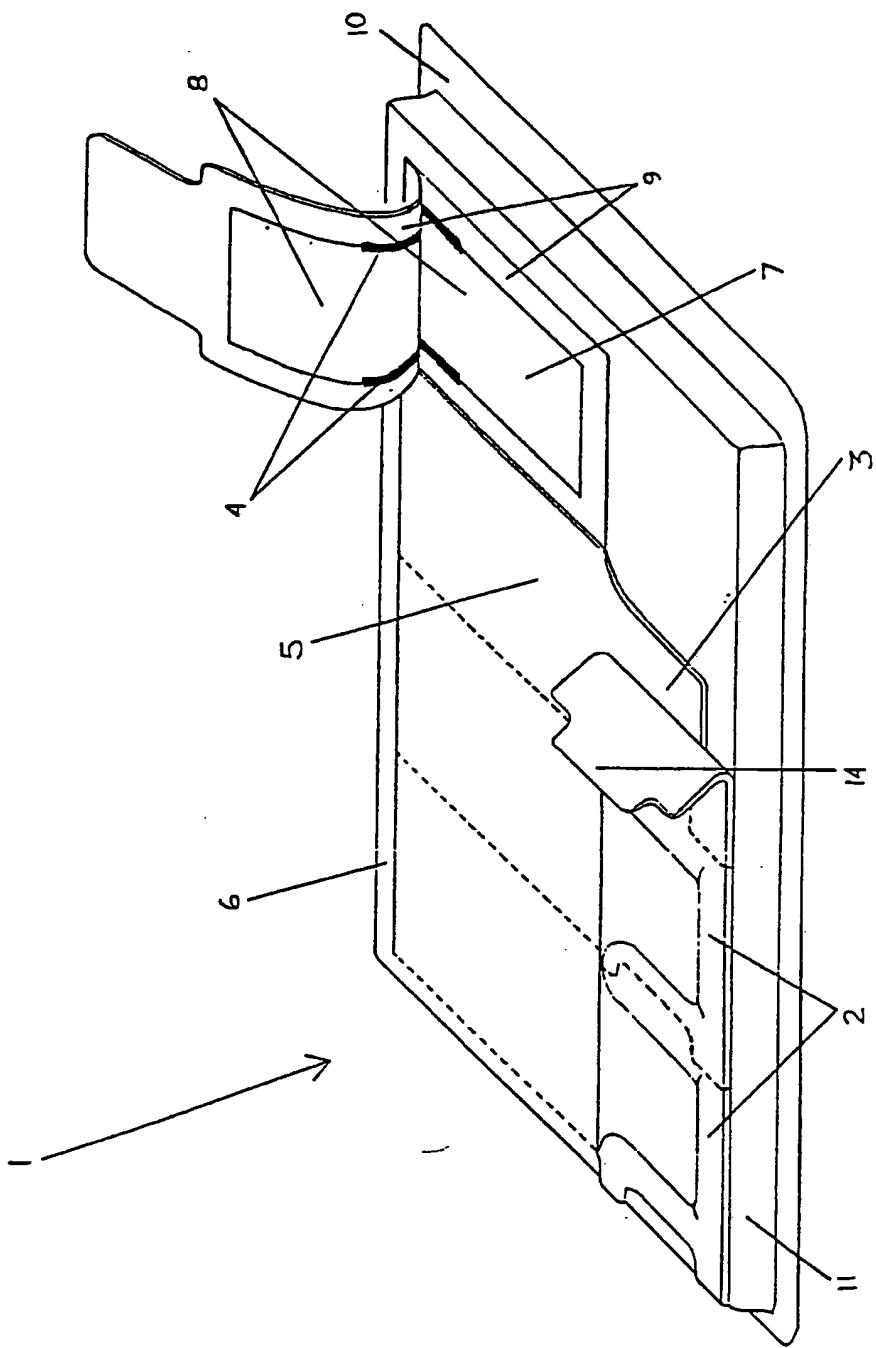
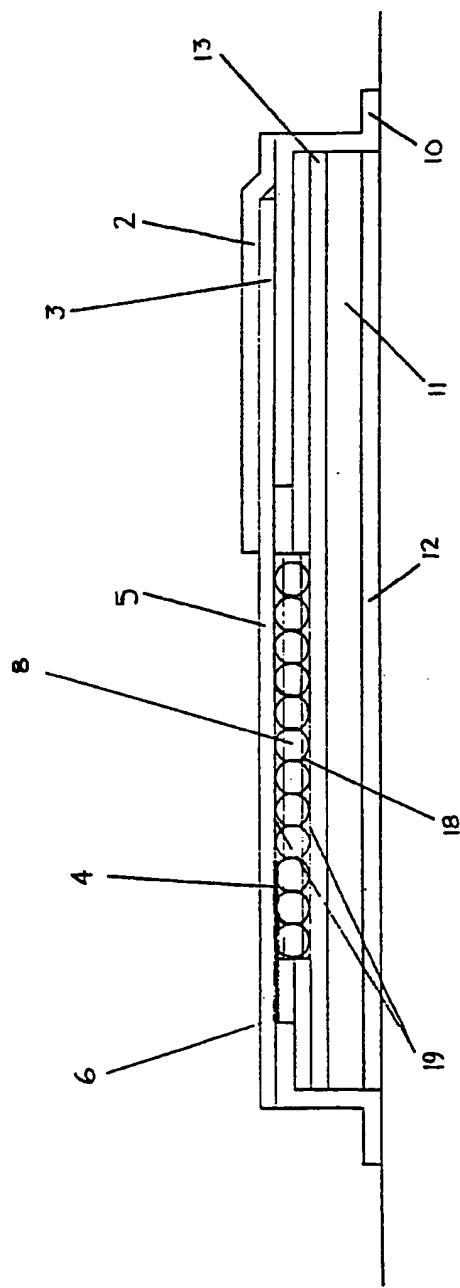


FIGURE 2



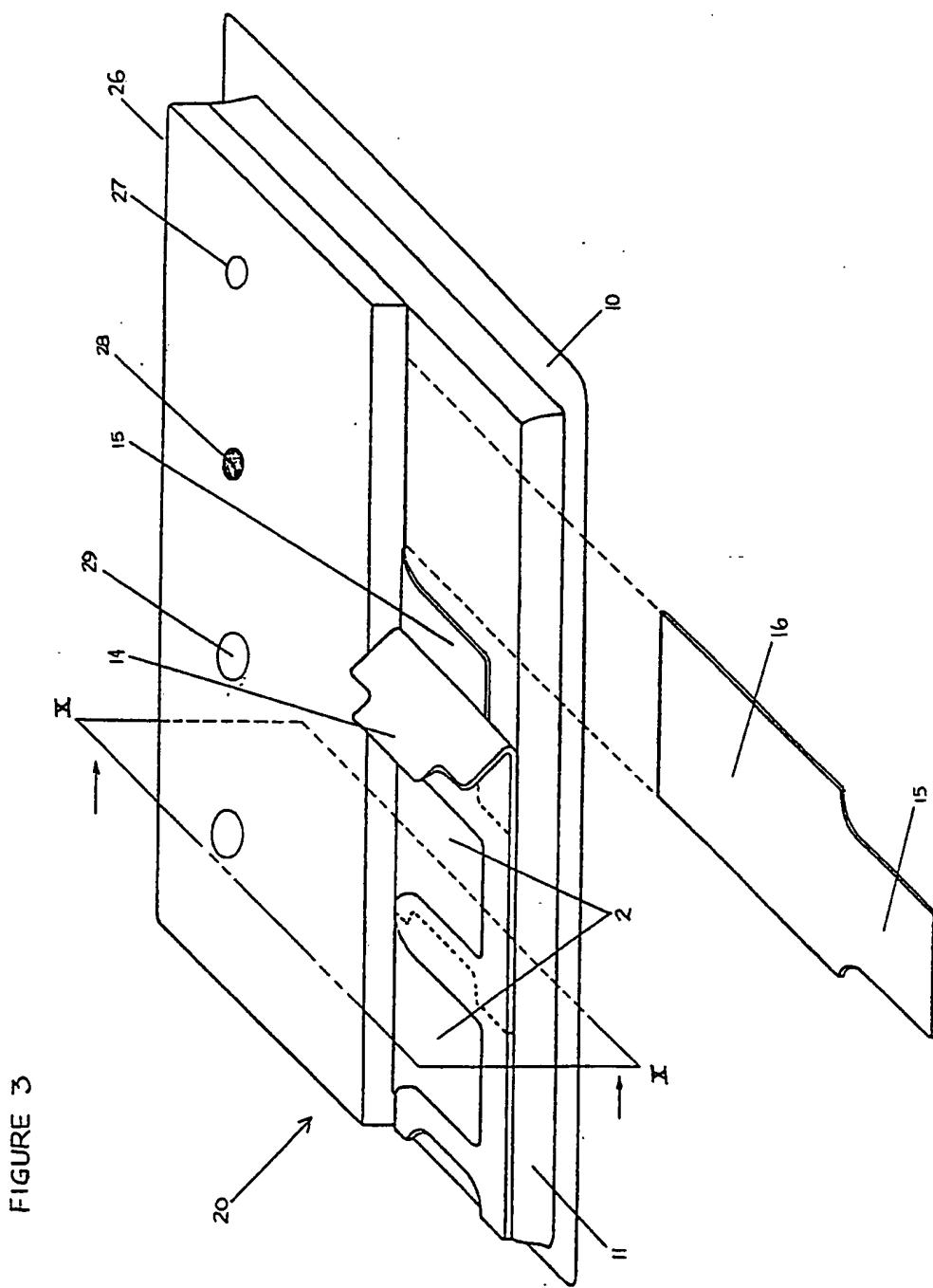
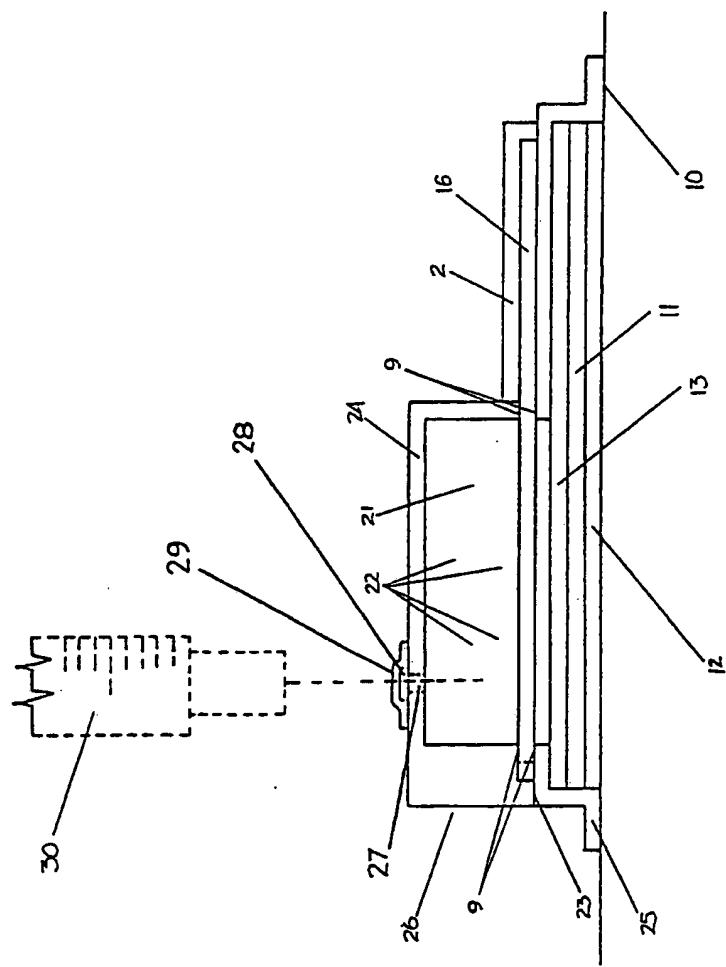


FIGURE 3

FIGURE 4



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/03088

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61F 13/00

US CL : 424/449

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/449, 447, 448; 602/41, 43, 52, 54, 57, 58, 63, 901

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS: Transdermal, bandage, patch, aminoguanidine, laurocapram, azone, insulin, microencapsulation, indicator, dye

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,573,996 (KWIATEK ET AL) 04 MARCH 1986; See column 6, lines 27-30; column 9, line 39 through column 10, line 1; column 11, lines 12 and 44-68.	1-13
Y	US, A, 4,666,441 (ANDRIOLA ET AL) 19 MAY 1987; See column 2, lines 55-67; column 3, line 45 through column 4, line 12.	14, 15
Y	US, A, 5,028,435 (KATZ ET AL) 02 JULY 1991 See column 3, lines 58-67; column 5, lines 56-62; column 7, lines 22-31.	16, 17
Y	US, A, 4,904,475 (GALE ET AL) 27 FEBRUARY 1990; See column 3, lines 20-60; column 4, lines 53-60.	18,19,22,23

<input checked="" type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
24 MAY 1993	19 JUL 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer D. GABRIELLE PHELAN <i>G. B. Phelan</i> Telephone No. (703) 308-2351
Facsimile No. NOT APPLICABLE	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/03088

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages.	Relevant to claim No.
Y	US, A, 4,917,676 (HEIBER ET AL) 17 APRIL 1990; See column 2, lines 29-37; column 3, lines 45-47; column 5, lines 29-61.	18,19,22,23
Y	US, A, 4,460,368 (ALLISON ET AL) 17 JULY 1984; See column 6, lines 18-25.	17
Y	US, A, 5,071,704 (FISCHEL-GHODSIAN) 10 DECEMBER 1991; See column 4, lines 9-21.	2
Y	US, A, 4,917,688 (NELSON ET AL) 17 APRIL 1990; See column 2, lines 47-62; column 3, lines 35-68.	20,21

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.